



UNIVERSITÀ
DEGLI STUDI
FIRENZE

FLORE

Repository istituzionale dell'Università degli Studi di Firenze

The burden of cutaneous adnexal carcinomas and the risk of associated squamous cell carcinoma: a population-based study

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

The burden of cutaneous adnexal carcinomas and the risk of associated squamous cell carcinoma: a population-based study / De Giorgi V.; Salvati L.; Barchielli A.; Caldarella A.; Gori A.; Scarfi F.; Savarese I.; Pimpinelli N.; Urso C.; Massi D.. - In: BRITISH JOURNAL OF DERMATOLOGY. - ISSN 0007-0963. - ELETTRONICO. - 180:3(2019), pp. 565-573. [10.1111/bjd.17321]

Availability:

This version is available at: 2158/1160655 since: 2019-07-07T10:52:37Z

Publisher:

WILEY

Published version:

DOI: 10.1111/bjd.17321

Terms of use:

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

Publisher copyright claim:

(Article begins on next page)

Article type : Original Article

The burden of cutaneous adnexal carcinomas and the risk of associated squamous cell carcinoma: a population-based study

V. De Giorgi^{1,2}, L. Salvati¹, A. Barchielli³, A. Caldarella³, A. Gori², F. Scarfi¹, I. Savarese¹, N. Pimpinelli¹, C. Urso⁴ and D. Massi⁵

¹Dermatologic Clinic, University of Florence, Florence, Italy

²Cancer Research "Attilia Pofferi" Foundation, Pistoia, Italy

³Clinical Epidemiology, Institute for Study and Cancer Prevention, Florence, Italy

⁴Dermatopathology Study Center of Florence, Florence, Italy

⁵Division of Pathological Anatomy, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy

Funding sources: None

Conflicts of Interest: None declared.

Keywords: epidemiology, survival, cutaneous adnexal carcinoma, skin appendageal tumors, rare skin cancer, squamous cell carcinoma, skin adnexal, porocarcinoma, sebaceous carcinoma, follow-up.

Corresponding author: Vincenzo De Giorgi, MD

E-mail: vincenzo.degiorgi@unifi.it

What's already known about this topic?

Cutaneous adnexal carcinomas are rare tumors, but their incidence is increasing. Their rarity prevents from gaining sufficient clinico-pathological experience: CACs can be a diagnostic challenge due to mostly non-specific clinical presentation and histopathological variety that often requires specific expertise for a definite diagnosis.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.17321

This article is protected by copyright. All rights reserved.

What does this study add?

CAC incidence increased from 2.5 in 1985-87 to 19 per million person-years in 2009-10; from 1997 it constantly increased rising up to 159% in 2010. In patients with cutaneous adnexal carcinoma, the risk of SCC is 34-times higher than in general population. Considering demographic evolution with progressive population's ageing and higher CACs' incidence among elderly, it is reasonable to expect a further increase in the future.

Abstract

Background: Recent studies have shown an increasing incidence of cutaneous adnexal carcinomas (CACs) over the years.

Objective: The aim of our study was to evaluate incidence and survival of CACs and investigate their association with other skin neoplasms.

Methods: Population based study. Data on incident cases of CACs were obtained from the Tuscany Cancer Registry (TCR) between 1985 and 2010. In order to determine if the occurrence of squamous cell carcinoma (SCC) among patients with CAC is higher or lower than expected in the general population, standardized incidence ratio (SIR) was calculated.

Results: 242 patients with CAC were observed; age-standardized incidence rate was 3.8 cases per million person-years. From 1997 to 2010, crude-incidence rates increased by 159%. Age-specific incidence was higher in males over 80 year-old than females of the same age and younger individuals. Carcinomas of sweat gland origin prevailed; the most common histotype was porocarcinoma and the most frequently affected site was the head-neck. 88% of CACs was diagnosed at a localized stage. 5-year overall survival and disease-specific survival rates were 59% (95% CI 53-65) and 94% (95% CI 91-98), respectively. In observation cohort, number of SCC was significantly higher than expected as SIR resulted 33.7 ($p < 0.0001$).

Conclusion: Increasing incidence warrants awareness and early diagnosis of cutaneous adnexal carcinomas. Increased SCC incidence among patients with these tumors highlights relevance of careful skin examination and follow-up.

INTRODUCTION

Cutaneous adnexal carcinomas (CACs) are a wide and heterogeneous group of malignant skin neoplasms that differentiate towards one or more appendageal structures: apocrine and eccrine sweat glands, hair follicle and sebaceous gland.¹ Classification is based on apocrine-eccrine, follicular or sebaceous differentiation displayed on histopathological examination. CACs most often present as single nodules or asymmetric plaques, sometimes ulcerated, with variable growth-rate, lacking in distinctive dermoscopic features.²⁻⁵ They are rare tumors with age-standardized incidence rate of 5.1 per million person-years in the USA and 2.8 in Europe (5.3 in the Netherlands).⁶⁻⁹ In Italy crude incidence rate is 6.1 per million (1343 cases observed in 2000-10) with 424 new cases diagnosed in 2015 (3.4% of all skin tumors registered in the same period).⁵ Their rarity prevents from gaining sufficient clinico-pathological experience and definite diagnosis often requires specific expertise.^{10,11} However incidence of these tumors has increased in recent years both in the USA and in Europe.^{6,7,12} Remarkably the incidence temporal trend has been similar to that of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma.⁶ Complete surgical excision is the treatment of choice; treatment of metastatic disease is described only in case-reports and there is no consensus about the most suitable therapeutic regimen being CACs often poor responsive to traditional chemotherapy.¹³ The role of target therapy is under investigation.¹⁴ Adjuvant radiotherapy may play a role for regional or distant disease control.¹⁵ Therefore prognosis is generally good when the neoplasm is localized to the skin, but deteriorates when distant organs are involved.^{7,16,17}

The present study examined a 25-years time period (1985-2010) in order to evaluate the burden of CACs in terms of incidence and survival. Based on Tuscany Cancer Registry (TCR) reports, we evidenced the registration of multiple skin cancers in several patients with CAC. Since all occurred cases of SCC have been registered by TCR (1985-2010), while BCC cases are not registered regularly

yet, we decided to investigate the association between CAC and SCC. In order to determine if the incidence of SCC among patients with CAC is higher or lower than expected, given the general population and age distribution, standardized incidence ratio (SIR) was calculated.

MATERIALS AND METHODS

We obtained and reviewed all cases of CACs collected from January 1st 1985 to December 31st 2010 by the Tuscany Cancer Registry (TCR), a population-based cancer registry active in the Italian area of Florence and Prato (inhabitants 1.2 million, area 3879 square kilometers). The source population was 30.720.481 individuals. One participant could contribute with several CACs. Cases were followed-up until December 1st 2016 considering the date of death or the date of last access to regional health services for any reason. Registry structure and methods have been previously reported.¹⁸ The following morphological codes, according to World Health Organization's International Classification of Diseases for Oncology Third Edition (ICD-O-3), were considered: 8102/3, 8110/3, 8200/3, 8211/3, 8400-03/3, 8407-10/3, 8413/3, 8420/3, 8480-81/3, 8940/3.¹⁹ Cases with topographic code C44 (skin) were included. Paget's disease was excluded for non-homogeneous coding. The variables considered for each patient were gender, age, tumor stage, anatomical localization, treatment, metastasis, and other neoplasms. All data were de-identified and tracked using a registry code number. According to Surveillance, Epidemiology and End Results Program Registries (SEER) summary staging system, tumor stage was classified in localized, regional, and distant.²⁰ *In situ* tumors were also considered.

Statistical analysis

Incidence rates were expressed per 1 million person-years and age-adjusted to the European Standard Population using the direct method.^{21,22} Age-specific incidence rates and incidence rate ratios (IRR) were calculated. Age-standardized incidence rate (ASR) confidence interval (CI) was calculated using binomial approximation. The survival end points were 5-year overall survival (OS) and 5-year disease-specific survival (DSS) rates; these were calculated using the life-table method.²³ OS defines the time from CAC's diagnosis to death from any cause or last follow-up; DSS the time from diagnosis to death from CAC; disease-free survival (DFS) the time after primary treatment for CAC

ends that the patient survives without any signs or symptoms of that cancer. Disease-specific survival rates at 1 and 5 years indicate the proportion of patients who have not die due to CAC at 1 and 5 years from the date of diagnosis of the neoplasm; patients who died from other causes were censored.

In order to investigate if the occurrence of SCC among patients with CAC was higher or lower than expected, standardized incidence ratio (SIR) was calculated. SIR is defined as the ratio between the number of SCC observed in patients with CAC and the number of SCC expected in the observation period (1985-2010) based on general population age-specific incidence rates. Only first SCCs were included in calculating the SIR. Statistical analysis was performed using Stata software version 11 (Stata Corp, College Station, TX, USA). For evaluation of statistical significance, χ -square test was used.

RESULTS

242 CACs were registered, 132 (55%) males and 110 (45%) females (Table I). ASR was 3.8 per million person-years (95% CI 3.2-5.2) and 7.8 was the crude incidence rate. Incidence increased from 2.5 in 1985-87 to 19 in 2009-10; from 1997 it constantly increased rising up to 159% in 2010 (Figure 1). Age-specific incidence rates remarkably rose from 0.9 in people ageing 30-34 years to 118 in those aged 85 or older (Figure 2). The incidence was higher in males (8.9) than females (6.8) with an IRR of 1.3. No cases were found in under 25. No patients had multiple CACs.

Carcinomas with sweat gland differentiation prevailed (198 cases, 82%), followed by carcinomas with sebaceous differentiation (32 cases, 13%). Porocarcinoma represented the most common histotype (55%, Table II) and the most frequent entity among both males and females (50.8% and 60% of CACs diagnosed respectively). Other recorded histotypes were: sebaceous carcinoma (13%), hidradenocarcinoma (12%), apocrine carcinoma (5%), adenoid cystic carcinoma, microcystic adnexal carcinoma and adnexal carcinoma with follicular differentiation (3.7% each), eccrine carcinoma (2%), cutaneous adnexal carcinoma NOS (1.2%), mucinous carcinoma (0.4%, Table II).

Age at diagnosis ranged from 26 to 99 years and mean age was 76.5 (SD = 14.1), 81 considering porocarcinoma.

56% of CACs was localized on the head-neck region, especially the face, including eyelid, lip, and ear (Figure 3). In males most neoplasms presented on scalp (23% vs 10% in females), whereas in females on lower limbs (16% vs 8% in males) and on trunk (21% vs 14% in males, Table I). Considering all histotypes the most common site was the head-neck (Table II), except from apocrine carcinoma that in 5 out of 12 cases was localized on trunk, preferentially in axillary region (Figure 3). By all anatomical sites the most common histotype was porocarcinoma: it represented almost half of carcinomas arising on face (47%) and trunk (49%), 63% of those arising on scalp, and more than 80% of CACs on extremities (Table II).

88% of CACs was localized to the skin at diagnosis while 4.5% extended directly into surrounding tissues and/or involved regional lymph nodes (Table I). Only 2.5% was diagnosed at distant stage. In situ tumors represented 3.7% and they were all intraepidermal porocarcinomas (Table II).

During follow-up period (mean follow-up time 85 months), 11 CACs (5 localized and 6 regional) metastasized. Taking into account all CACs that metastasized during follow-up, DFS was 70.6 months (median 25). Regional stage carcinomas had 32 months DFS (median 22).

Metastases were more commonly observed in males (Table I), mainly due to CACs primitively located on head-neck (9/17) and with sweat gland differentiation, particularly porocarcinoma (Table II). Lung (7/17), skin (4/17), brain (3/17), and liver (2/17) were more commonly involved.

3 porocarcinomas and 1 sebaceous carcinoma of the upper eyelid (that invaded orbital structures), treated by radical surgical excision with negative margins, relapsed after 48.7 months (median 43.5).

Surgery was performed in 99% of patients. In selected cases adjuvant chemotherapy and/or radiotherapy were performed (Table I).

5-year OS and DSS rate were 59% (95%CI 53-65) and 94% (95%CI 91-98), as shown in Figure 4.

The median DSS was 27 months.

123 (50.8%) patients presented one or more other malignant tumor in their medical history: 61 patients had or had had an extracutaneous tumor, 96 a further skin cancer (including BCC, SCC, melanoma, Bowen disease, actinic keratosis, and Merkel cell carcinoma).

During observation period (TCR, 1985-2010), 36 (14.9%) patients presented at least one SCC, while 1.07 cases of SCC would be expected in the present cohort based on age-specific incidence rates. SIR resulted 33.71, p -value <0.0001 (i.e. observed SCCs were 33.71 times higher than expected). The histotypes of CACs associated with SCC are described in Table III. Taking into consideration SCC observed in patients with porocarcinoma, the two neoplasms arose on same anatomical region in 76% of cases, particularly on head region. Similar anatomical site concordance was equally observed in patients with other histological types. In 1/3 of cases SCC was diagnosed before CAC, in 1/3 at the same time and in 1/3 after (Table III). Mean age at diagnosis of SCC in patients with CAC was 82 years.

DISCUSSION

Even in the Italian area of Florence and Prato (TCR, 1985-2010), CACs are rare tumors as ASR is 3.8 per million person-years, which is higher than ASR reported in Southern Europe (2.5) but overlaps with that registered in Northern Europe ($p < 0.01$).^{6,7,8} Crude-incidence is 7.8 although it resulted 12.6 in 2000-10 twice the rate (6.1) described by Italian cancer report.⁹ Crude-incidence has increased over the years and fewer cases in 1994-96 are likely to be attributed to lower registration or coding system shift. There has been a steady increase in incidence with 159% change between 1997-98 and 2009-10 (Figure 1).

Different factors may justify increasing temporal trend as real increase of incident cases, but also diagnostic techniques' improvement via histopathological confirmation of all excised skin lesions, demographic evolution with population ageing (age-specific incidence peaks over 85 year-old) and finally greater awareness to skin cancer registration in recent decades. In support of real incidence boost of these tumors rather than improved diagnostic ability, Blake et al. demonstrated that such an increase applies to all tumor stages.⁶ In addition since their incidence trend is comparable to that reported for BCC, SCC, and melanoma it has been hypothesized that UV radiation may be implicated in CACs pathogenesis.^{6,7,24,25,26}

The excellent 5-year DSS (94%) can be explained by diagnosis of CACs predominantly at localized stage and efficacy of excisional surgery. It is higher than 5-year OS (59%) because more than half of CACs are found in people over 80 year-old who died for other causes not related to CAC. In general our survival rates are lower than those reported in the USA.¹⁶ This discrepancy may be due to older population (73% over 70 year-old in present study vs 49% in Martinez et al.) and delayed diagnosis (2.5% distant stage vs 1.7%). It is worth mentioning that our study population differs on sample size being that of Martinez et al. considerably bigger, nevertheless older age is a known cancer risk factor and elderly people have worse prognosis than younger ones. In fact DNA damage accumulates over time, resulting in malignant cellular transformation and immunosenescence that determines deficit of adaptive immunity and a protumorigenic inflammatory microenvironment.²⁷ Even fibroblasts' ability to scavenge oxygen free radicals is reduced in older skin with less protection against oxidative stress.²⁸ Diagnostic delay may also impact on survival, especially in elderly population where slow-growing skin lesions are often underestimated.

CACs' clinical presentation is heterogeneous, thus histopathological examination is mandatory representing the diagnostic gold standard. Incisional biopsy may not be representative of the tumor in its entirety, so an excisional biopsy is preferable. In the suspect of an adnexal carcinoma, it is necessary to avoid inappropriate destructive treatments, as there is risk of recurrence and metastasis. Pathological examination provides information about histotype, lymphatic and/or vascular

invasion, status of deep and lateral excision margins. Classification of CACs poses many difficulties considering synonyms and dignity of definition of some entities.²⁹⁻³¹ In our study carcinomas with sweat gland differentiation are the most common category (82%), followed by tumors with sebaceous differentiation (Table II) according to previous epidemiological studies.^{6,7,9} Among tumors with sweat gland differentiation, the most frequent histotype is porocarcinoma representing 55% of all CACs, far above 7% reported by SEER Registries.⁶ Porocarcinoma is also more common than sebaceous carcinoma that is the most frequent CAC diagnosed in both Dutch and American populations (13% vs 25% and 35% respectively).^{6,7} Since etiology of CACs remains still unknown, the comparison of different epidemiological patterns for specific histological types can provide useful insights.⁶ Different histotype distribution may depend on selection and diverse composition of observed population as a result of exposure to different risk factors both environmental (geographic area, exposure to solar UV radiation, atmospheric pollution) and individual (concomitant diseases, immunosuppression, viral infections).³²⁻³⁶

The most frequent localization in sun-exposed areas (head-neck region with predominant onset on male scalp) as happens in NMSC, suggests a possible common etiopathogenesis represented by chronic sun-exposure.^{6,7,37}

An interesting result is that in the examined population we found a higher number of SCCs than expected based on age specific population incidence rates with a SIR of 33.7. It means that patients with CAC have a risk of developing an SCC 34-times higher than general population. Surprisingly, SCC were localized in the same anatomic region of CAC, particularly the head (Table III). To date only a few case reports have described the association of CAC and SCC in the same patient and in only one case, an 86-year-old patient history of cumulative solar UV-exposure has been documented.^{38,39} Cases in association with Bowen's disease or arising in the site of a previous Bowen have also been reported;⁴⁰⁻⁴² this finding, difficult to explain, may be due to the close histologic resemblance between Bowen's disease and *in situ* porocarcinoma. Concomitant onset of CAC and SCC in sun-exposed areas and independent distribution over time in the way that now SCC and now

CAC arises, emphasizes the concept of field cancerization.^{43,44} Strong site coincidence could be related to exposure to common risk factors such as solar UV radiation or other factors (i.e. genetic) not yet known. Recently, mutations compatible with sun radiation damage (UV mutational signature) and similar to those found in melanoma of the skin, SCC, and Merkel polyomavirus-negative cell carcinoma have been identified in porocarcinomas of the head.^{37,45} In the present study, surveillance bias could also represent part of the explanation for the similar anatomical localizations of CAC and SCC. However, the TCR does not collect information about neither initial nor follow-up visits, so it is not known how much closely or with what frequency patients have been followed-up or how much carefulness was put in the medical examination. Being male and elder represents risk factor for both CAC and SCC: this is important in guiding dermatologists in clinically approaching these patients at initial visit and follow-up.

To date for patients with CAC neither modality nor duration of follow-up has been established; on the basis of our results we propose to investigate patients as described in Figure 5. During follow-up other skin lesions eventually associated should be checked, especially considering SCC higher incidence in patients with CAC. Attention should be drawn to elderly male patients with porocarcinoma arising on head and patients with regional tumor stage at diagnosis. Disease-specific deaths' concentration in the first 3 years from diagnosis (median DSS 27 months) highlights the opportunity of a close follow-up. It would be wise to prolong follow-up until 5 years from diagnosis given that recurrences observed occurred after 48.7 months. In patients with regional stage tumor attention should be kept in the first 2 years of follow-up, as median DFS was 22 months in this group. However, these considerations should be evaluated in the light of two main limits: relatively small sample size, which determines a strong statistical oscillation and influence of competitive mortality for other causes.

It would be desirable to create a global register of rare skin cancers in order to allow a precise knowledge of the burden of CACs worldwide,^{47,48} and include a section dedicated to these tumors in the guidelines of leading dermatology societies so to achieve uniform treatment and management, since rarity of CACs must not be excuse of less attention.

CONCLUSION

Considering demographic evolution with progressive population's ageing and higher CACs' incidence among elderly, it is reasonable to expect a further increase in the future. Therefore early diagnosis and proper treatment is crucial. Do never underestimate new onset of skin lesions in sun-exposed areas in elderly, especially in those who have history of adnexal carcinoma.

Abbreviations

ASR age-standardized incidence rate

CAC cutaneous adnexal carcinoma

CI confidence interval

DFS disease-free survival

DSS disease-specific survival

IRR incidence rate ratio

NMSC non melanoma skin cancer

OS overall survival

SCC squamous cell carcinoma

SD standard deviation

SIR standardized incidence ratio

TCR Tuscany Cancer Registry

References

1. LeBoit PE, Burg G, Weedon D, Sarasin A, editors. World Health Organization Classification of Tumours. Pathology and Genetics of Skin Tumours. Lyon: IARC Press; 2006.
2. Zelger B, Kazakov DV, Zelger BG. [Clinical presentation of cutaneous adnexal tumors]. Pathologie. 2014;35(5):487-496.
3. Alsaad KO, Obaidat NA, Ghazarina D. Skin adnexal neoplasms—part 1: An approach to tumours of the pilosebaceous unit. J Clin Pathol. 2007;60(2):129-144.

4. Obaidat NA, Alsaad KO, Ghazarian D. Skin adnexal neoplasms—part 2: An approach to tumours of cutaneous sweat glands. *J Clin Pathol.* 2007;60(2):145-159.
5. Zalaudek I, Kreusch J, Giacomel J, Ferrara G, Catricalà C, Argenziano G. How to diagnose nonpigmented skin tumors: a review of vascular structures seen with dermoscopy: part II. Nonmelanocytic skin tumors. *J Am Acad Dermatol.* 2010;63(3):377-386.
6. Blake PW, Bradford PT, Devesa SS, Toro JR. Cutaneous appendageal carcinoma incidence and survival patterns in the United States: a population-based study. *Arch Dermatol.* 2010;146(6):625-632.
7. Stam H, Lohuis PJ, Zupan-Kajcovski B, Wouters MW, van der Hage JA, Visser O. Increasing incidence and survival of a rare skin cancer in the Netherlands. A population-based study of 2,220 cases of skin adnexal carcinoma. *J Surg Oncol.* 2013;107(8):822-827.
8. Mallone S, De Vries E, Guzzo M, Midena E, Verne J, Coebergh JW, Marcos-Gragera R, Ardanaz E, Martinez R, Chirilaque MD, Navarro C, Virgili G; The RARECARE WG. Descriptive epidemiology of malignant mucosal and uveal melanomas and adnexal skin carcinomas in Europe. *Eur J Cancer.* 2012;48:1167-1175.
9. AIRTUM Working Group, Busco S, Buzzoni C, Mallone S, Trama A, Castaing M, Bella F, Amodio R, Bizzoco S, Cassetti T, Cirilli C, Cusimano R, De Angelis R, Fusco M, Gatta G, Gennaro V, Giacomini A, Giorgi Rossi P, Mangone L, Mannino S, Rossi S, Pierannunzio D, Tavilla A, Tognazzo S, Tumino R, Vicentini M, Vitale MF, Crocetti E, Dal Maso L. Italian Cancer Figures - Report 2015. The burden of rare cancers in Italy. *Epidemiol Prev.* 2016;40(1 Suppl 2):1-120.
10. Cardoso JC and Calonje E. Malignant sweat gland tumours: an update. *Histopathology.* 2015;67(5):589-606.
11. Danialan R, Mutyambizi K, Aung P, Prieto VG, Ivan D. Challenges in the diagnosis of cutaneous adnexal tumours. *J Clin Pathol.* 2015;68(12):992-1002.
12. [dataset] RARECAREnet project; 2017. External link <http://app.rarecaren.net/>

13. De Iuliis F, Amoroso L, Taglieri L, Vendittozzi S, Blasi L, Salerno G, Lanza R, Scarpa S. Chemotherapy of rare skin adnexal tumors: a review of literature. *Anticancer Res.* 2014;34(10):5263-5268.
14. Dias-Santagata D, Lam Q, Bergethon K, Baker GM, Iafrate AJ, Rakheja D, Hoang MP. A potential role for targeted therapy in a subset of metastasizing adnexal carcinomas. *Mod Pathol.* 2011;24(7):974-982.
15. Miller DH, Peterson JL, Buskirk SJ, Vallow LA, Ta R, Joseph R, Krishna M, Ko SJ, Tzou KS. Management of Metastatic Apocrine Hidradenocarcinoma with Chemotherapy and Radiation. *Rare Tumors.* 2015;7(3):6082.
16. Martinez SR, Barr KL, Canter RJ. Rare tumors through the looking glass: an examination of malignant cutaneous adnexal tumors. *Arch Dermatol.* 2011;147(9):1058-1062.
17. Avraham JB, Villines D, Maker VK, August C, Maker AV. Survival after resection of cutaneous adnexal carcinomas with eccrine differentiation: risk factors and trends in outcomes. *J Surg Oncol.* 2013;108(1):57-62.
18. Paci E, Crocetti E, Benvenuti A, Buzzoni C, Caldarella A, Giovannetti L, Giusti F, Intrieri T, Manneschi G, Miccinesi G, Sacchetti C: Cancer incidence in Florence and Prato (1998–2002). In: Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P, eds. *Cancer incidence in five continents, Volume IX.* Lyon: IARC Scientific Publications No. 160; 2007:319.
19. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, eds. *International Classification of Diseases for Oncology, 3rd ed.* Geneva: World Health Organization; 2013.
20. Young JL Jr, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA, eds. *SEER Summary Staging Manual - 2000: Codes and Coding Instructions*, National Cancer Institute. Bethesda, MD: NIH Pub. No. 01-4969; 2001
21. Waterhouse J, Muir C, Correa P, Powell J, eds. *Cancer incidence in five continents, Volume III.* Lyon: IARC Scientific Publications No. 15; 1976.
22. Boyle P and Parkin DM. Statistical methods for registries. In: Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG, editors. *Cancer registration principles and methods.* Lyon: IARC Scientific publication No. 95; 1991:126-158.

23. Parkin DM and Hakulinen T. Analysis of survival. In: Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG, editors. Cancer registration principles and methods. Lyon: IARC Scientific publication No. 95; 1991:159-176.
24. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer - the role of sunlight. *Adv Exp Med Biol.* 2008;624:89-103.
25. Apalla Z, Lallas A, Sotiriou E, Lazaridou E, Ioannides D. Epidemiological trends in skin cancer. *Dermatol Pract Concept.* 2017;7(2):1-6.
26. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B.* 2001;63(1-3):8-18.
27. Wellbrock C. Melanoma and the Microenvironment - Age Matters. *N Engl J Med.* 2016;375(7):696-698.
28. Kaur A, Webster MR, Marchbank K, Behera R, Ndoye A, Kugel CH 3rd, Dang VM, Appleton J, O'Connell MP, Cheng P, Valiga AA, Morissette R, McDonnell NB, Ferrucci L, Kossenkova AV, Meeth K, Tang HY, Yin X, Wood WH 3rd, Lehrmann E, Becker KG, Flaherty KT, Frederick DT, Wargo JA, Cooper ZA, Tetzlaff MT, Hudgens C, Aird KM, Zhang R, Xu X, Liu Q, Bartlett E, Karakousis G, Eroglu Z, Lo RS, Chan M, Menzies AM, Long GV, Johnson DB, Sosman J, Schilling B, Schadendorf D, Speicher DW, Bosenberg M, Ribas A, Weeraratna AT. sFRP2 in the aged microenvironment drives melanoma metastasis and therapy resistance. *Nature.* 2016;532(7598):250-254.
29. Mentzel T, Ritten A. [Adnexal skin tumours]. *Pathologe.* 2014;35(5):412.
30. Kazakov DV, McKee PH, Michal M, Kacerovska D. Cutaneous Adnexal Tumors. Philadelphia, PA: Wolters Kluwer Health, Lippincott Williams & Wilkins; 2012.
31. Urso C. Porocarcinoma: an exceedingly rare tumor or a tumor eclipse phenomenon? *Hum Pathol.* 2013;44(3):448-449.
32. Bauer A, Beissert S, Knuschke P. [Prevention of occupational solar UV radiation-induced epithelial skin cancer]. *Hautarzt.* 2015;66(3):173-178.
33. Miligi L, Benvenuti A, Legittimo P, Badiali AM, Cacciarini V, Chiarugi A, Crocetti E, Alberghini Maltoni S, Pinto I, Zipoli G, Grifoni D, Carnevale F, Pimpinelli N, Cherubini Di Simplicio F, Poggiali

- S, Sartorelli P, Sirna R, Amati R, Centi L, Festa G, Fiumalbi C, Fedi A, Giglioli S, Mancini R, Panzone T, Petrioli G, Trombetti A, Volpi D. [Solar ultraviolet radiation risk in outdoor workers: a specific project of Tuscany Region (Italy)]. *Epidemiol Prev.* 2013;37(1):51-59.
34. Harwood CA, McGregor JM, Swale VJ, Proby CM, Leigh IM, Newton R, Khorshid SM, Cerio R. High frequency and diversity of cutaneous appendageal tumors in organ transplant recipients. *J Am Acad Dermatol.* 2003;48(3):401-408.
35. Lanoy E, Dores GM, Madeleine MM, Toro JR, Fraumeni JF Jr, Engels EA. Epidemiology of nonkeratinocytic skin cancers among persons with AIDS in the United States. *AIDS.* 2009;23(3):385-393.
36. Lanoy E, Costagliola D, Engels EA. Skin cancers associated with HIV infection and solid- organ transplantation among elderly adults. *Int J Cancer.* 2010;126(7):1724-1731.
37. Harms PW, Hovelson DH, Cani AK, Omata K, Haller MJ, Wang ML, Arps D, Patel RM, Fullen DR, Wang M, Siddiqui J, Andea A, Tomlins SA. Porocarcinomas harbor recurrent HRAS-activating mutations and tumor suppressor inactivating mutations. *Hum Pathol.* 2016;51:25-31.
38. Cribier B, Lipsker D, Grosshans E. Eccrine porocarcinoma, tricholemmal carcinoma and multiple squamous cell carcinomas in a single patient. *Eur J Dermatol.* 1999;9(6):483-486.
39. Helmer A, Merk HF, Megahed M, Abuzahra F. [Eccrine porocarcinoma together with multiple other epithelial skin tumours]. *Hautarzt.* 2006;57(12):1120-1121.
40. Hoshina D, Akiyama M, Hata H, Aoyagi S, Sato-Matsumura KC, Shimizu H. Eccrine porocarcinoma and Bowen's disease arising in a seborrheic keratosis. *Clin Exp Dermatol.* 2007;32(1):54-56.
41. Lowney AC, Mc Aleer MA, O'Connor K, Fitzgibbon JF, Bourke JF. Eccrine porocarcinoma arising within an area of Bowen disease. *Clin Exp Dermatol.* 2012;37(2):136-138.
42. Zheng LQ, Han XC, Huang Y, Li HW, Niu XD, Li J. Porocarcinoma coexisting at a site of Bowen disease in a 63-year-old woman. *Clin Exp Dermatol.* 2015;40(3):293-297.
43. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. *Cancer Res.* 2003;63(8):1727-1730.

44. Kanjilal S, Strom SS, Clayman GL, Weber RS, el-Naggar AK, Kapur V, Cummings KK, Hill LA, Spitz MR, Kripke ML, Ananthaswamy HN. p53 mutations in nonmelanoma skin cancer of the head and neck: molecular evidence for field cancerization. *Cancer Res.* 1995;55(16):3604-3609.
45. Pickering CR, Zhou JH, Lee JJ, Drummond JA, Peng SA, Saade RE, Tsai KY, Curry JL, Tetzlaff MT, Lai SY, Yu J, Muzny DM, Doddapaneni H, Shinbrot E, Covington KR, Zhang J, Seth S, Caulin C, Clayman GL, El-Naggar AK, Gibbs RA, Weber RS, Myers JN, Wheeler DA, Frederick MJ. Mutational landscape of aggressive cutaneous squamous cell carcinoma. *Clin Cancer Res.* 2014;20(24):6582-6592.
46. Anderson HL, Joseph AK. A pilot feasibility study of a rare skin tumor database. *Dermatol Surg.* 2007;33(6):693-696.
47. Frieden TR. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. *N Engl J Med.* 2017;377(5):465-475.

Figure legend

Figure 1. "Trends in crude-incidence rates of cutaneous adnexal carcinomas in Tuscany Cancer Registry, 1985-2010."

Figure 2. "Age-specific incidence curves for cutaneous adnexal carcinomas in males, females and both genders in Tuscany Cancer Registry, 1985-2010."

Figure 3. "Anatomic location by gender and histotype of cutaneous adnexal carcinomas in Tuscany Cancer Registry, 1985-2010."

Figure 4. "Overall survival and disease-specific survival rates among patients with cutaneous adnexal carcinoma in Tuscany Cancer Registry, 1985-2010."

Figure 5. "Follow-up scheme based on TCR analysis, 1985-2010. Patients with CAC should be followed up every 6 months in the first 2 years and every year up to 5 years after initial diagnosis. Follow-up should include: complete history account, status and skin examination with palpation of main lymph node stations; ultrasonography of loco-regional draining lymph nodes and instrumental investigation of most common metastatic sites (i.e. lung, chest x-ray at diagnosis and the following year). Patient clinical status must guide choice and appropriateness of instrumental examination."

Table legend

Table I. “Features of cutaneous adnexal carcinomas in Tuscany Cancer Registry, 1985-2010”

Table II. “Cutaneous adnexal carcinomas according to histological type: cases distribution by gender, anatomical localization, tumor stage at diagnosis and metastases (TCR, 1985-2010).”

Table III. “Association between cutaneous adnexal carcinoma and squamous cell carcinoma in Tuscany Cancer Registry, 1985-2010: SCC cases observed by CAC histological type, temporal relation of SCC with CAC’s diagnosis and site match.”

Table I. "Features of cutaneous adnexal carcinomas in Tuscany Cancer Registry, 1985-2010"

	Gender		
	Males and Females No. (%)	Males No. (%)	Females No. (%)
Year of diagnosis			
1985-1990	27 (11)	17 (13)	10 (9)
1991-1995	27 (11)	19 (14)	8 (7)
1996-2000	31 (13)	15 (11)	16 (15)
2001-2005	63 (26)	27 (20)	36 (33)
2006-2010	94 (39)	54 (41)	40 (36)
All years	242 (100)	132 (100)	110 (100)
Age at diagnosis			
<55	20 (8)	7 (5)	13 (12)
55-69	39 (16)	26 (20)	13 (12)
70-84	94 (39)	57 (43)	37 (34)
>85	89 (37)	42 (32)	47 (43)
Primary site (topographical code ICD-O-3)			
Lip (C440)	3 (1)	2 (2)	1 (1)
Eyelid (C441)	12 (5)	7 (5)	5 (5)
Ear (C442)	15 (6)	12 (9)	3 (3)
Head and neck (C443-4)	105 (43)	59 (45)	46 (42)
Trunk (C445)	41 (17)	18 (14)	23 (21)
Upper limb (C446)	18 (7)	11 (8)	7 (6)
Lower limb (C447)	28 (12)	10 (8)	18 (16)
Overlapping (C448)	2 (1)	1 (1)	1 (1)
Unknown (C449)	18 (7)	12 (9)	6 (5)
Stage			
In situ	9 (4)	5 (4)	4 (4)
Localized	214 (88)	118 (89)	96 (87)
Regional	11 (4)	3 (2)	8 (7)
Distant	6 (2)	5 (4)	1 (1)
Unknown	2 (1)	1 (1)	1 (1)
Treatment			
Surgery	230 (95)	126 (95)	104 (95)
Surgery + chemotherapy	4 (2)	2 (2)	2 (2)
Surgery + radiotherapy	4 (2)	2 (2)	2 (2)
Surgery + chemotherapy + radiotherapy	1 (0)	0 (0)	1 (1)
Radiotherapy	1 (0)	1 (1)	0 (0)
No treatment	2 (1)	1 (1)	1 (1)
Metastasis*			
	17 (7)	10 (8)	7 (6)
Lymph node dissection*			
	14 (6)	3 (2)	11 (10)

*include: at time of diagnosis and during follow-up

Table II. "Cutaneous adnexal carcinomas distribution according to histological type: cases distribution by gender, anatomical localization, tumor stage at diagnosis and metastases (TCR, 1985-2010)."

Histological type (ICD-O-3)	No.cases	Gender		Anatomical localization					Tumor stage at diagnosis					Metastases
		Males	Females	Face	Scalp	Trunk	Limbs (upper; inferior) Multisite/ NOS	In situ	Localized	Regional	Distant	Unknown		
Porocarcinoma (8409/3)	133	67	66	44	26	20	38 (15;23)	5	9	114	7	2	1	8
Sebaceous carcinoma (8410/3)	32	20	12	17	3	3	1 (1;0)	8	0	31	0	0	1	0
Hidradenocarcinoma (8400/3, 8402/3)	29	16	13	12	4	8	5 (1;4)	0	0	26	2	1	0	3
Apocrine carcinoma (8401/3)	12	6	6	3	1	5	1 (0;1)	2	0	9	1	2	0	3
Adenoid cystic carcinoma (8200/3)	9	5	4	5	0	3	0	1	0	8	1	0	0	2
Microcystic adnexal carcinoma (8407/3)	9	6	3	4	3	2	0	0	0	9	0	0	0	0
CAC with follicular differentiation (8102/3, 8110/3)	9	7	2	5	1	0	1 (1;0)	2	0	9	0	0	0	0
Eccrine carcinoma (8413/3)	5	3	2	3	2	0	0	0	0	4	0	1	0	1
CAC NOS (8390/3)	3	1	2	1	1	0	0	1	0	3	0	0	0	0
Mucinous carcinoma (8480/3)	1	1	0	0	0	0	0	1	0	1	0	0	0	0
Total (all histological types)	242	132	110	94	41	41	46 (18;28)	20	9	214	11	6	2	17

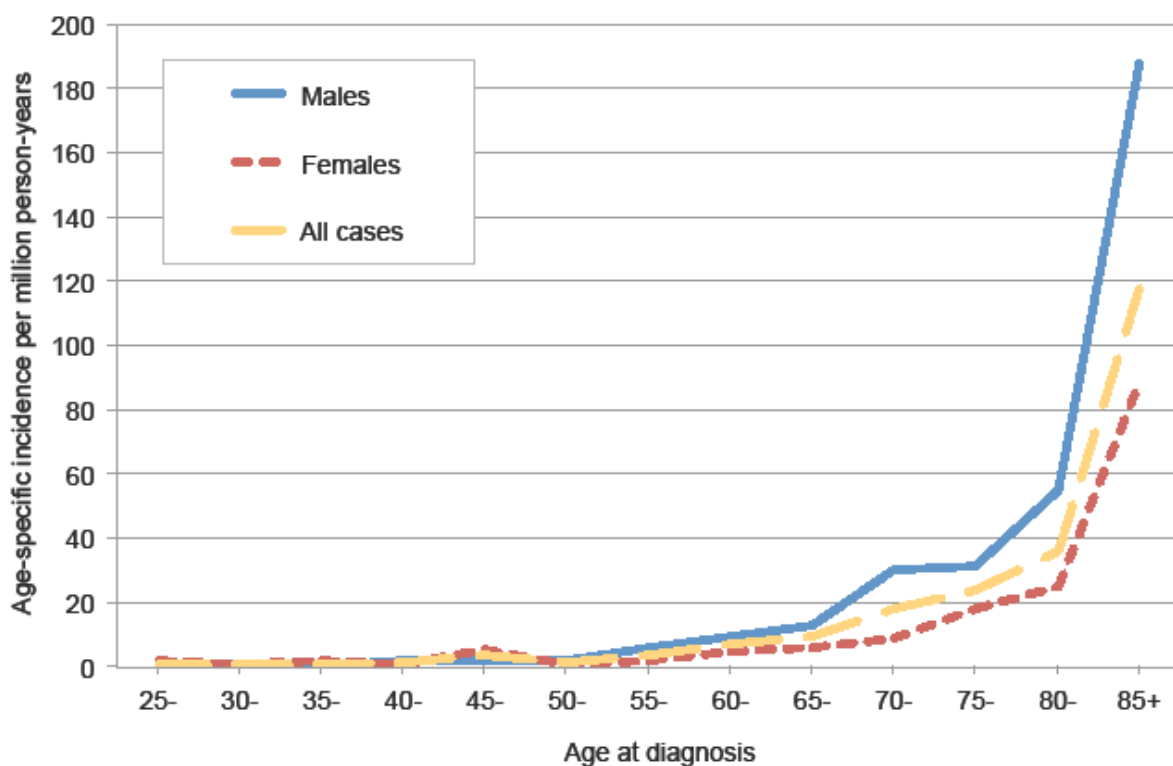
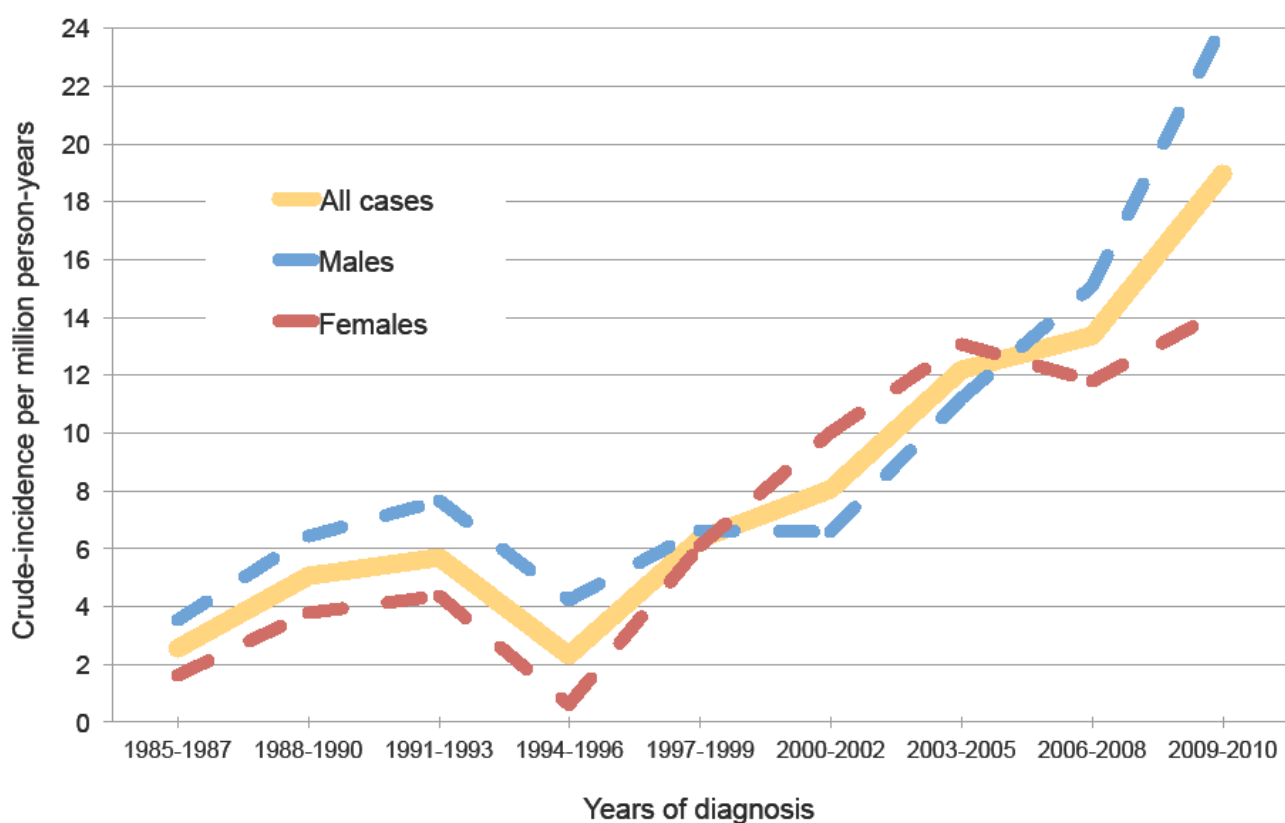
NOS, *not otherwise specified*

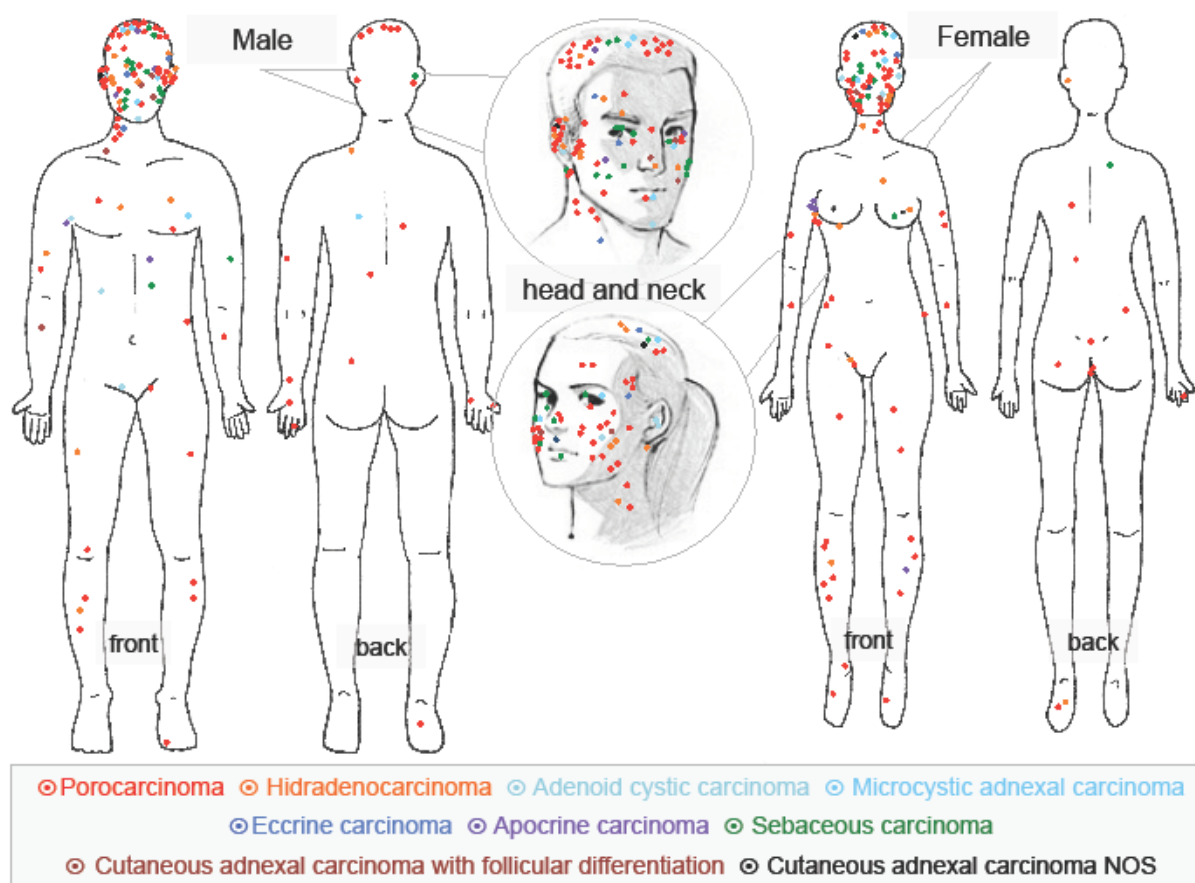
Table III. “Association between cutaneous adnexal carcinoma and squamous cell carcinoma in Tuscany Cancer Registry, 1985-2010: SCC cases observed by CAC histological type, temporal relation of SCC with CAC’s diagnosis and site match.”

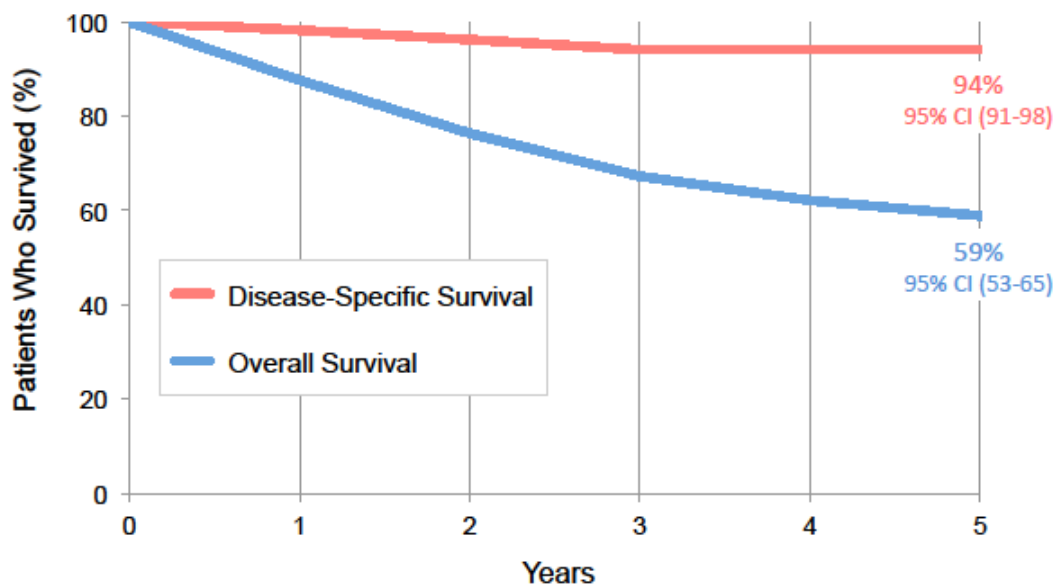
Histological type	SCC observed (males;females)	SCC diagnosis (compared to CAC)			SCC and CAC site match(SCC observed per site)		
		Earlier	Concomitant	Later	All sites	Head	Limbs
Porocarcinoma	21 (15;6)	8	8	5	16(19*)	15(16)	1(3)
Hidradenocarcinoma	7 (6;1)	1	2	4	6(7)	6(7)	0(0)
Sebaceous carcinoma	6 (4;2)	2	1	3	3(6)	2(4)	1(2)
CAC with follicular differentiation	1 (1;0)	1	0	0	1(1)	1(1)	0(0)
Microcystic adnexal carcinoma	1 (1;0)	1	0	0	1(1)	1(1)	0(0)
All histological types	36 (27;9)	13	11	12	27(34*)	25(29)	2(5)

SCC, *squamous cell carcinoma*; CAC, *cutaneous adnexal carcinoma*

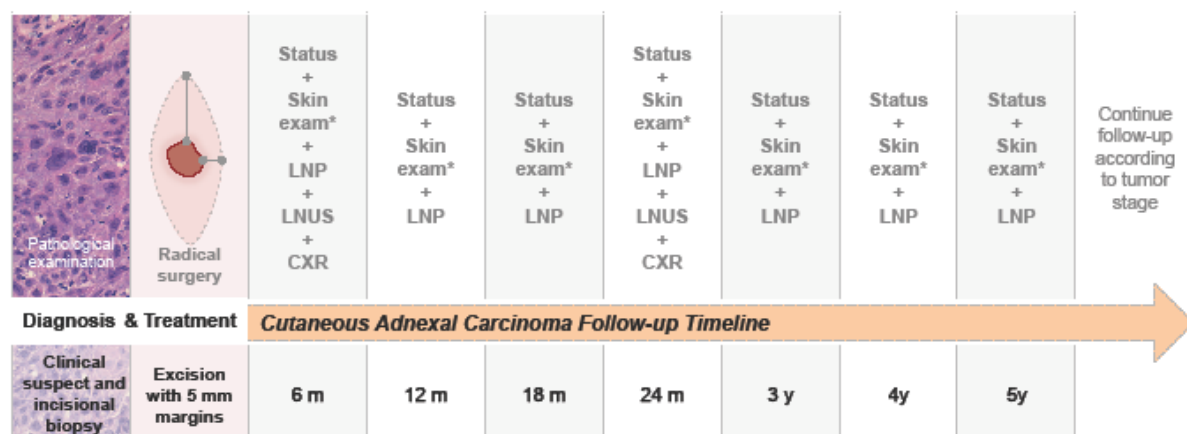
*Unknown localization for 2 porocarcinomas.







Disease-Specific Survival					
No. at Risk	228.5	199.5	174.5	155	144.5
No. of Events	4	4	4	0	0
Overall Survival					
No. at Risk	241.5	211	183.5	161	148.5
No. of Events	30	27	22	12	8



LNP lymphnodes palpation; LNUS regional lymphnodes ultrasound; CXR chest x-ray.

* At skin examination attention should be drawn to new-onset lesion, especially in the elderly and on the head region.